IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	David H. Munn et al.
Appl. No.:	10/660,131
Art Unit:	1647
Filed:	September 11, 2003
Examiner:	Regina M. DeBerry
For:	Chemokine Receptor Antagonists as Therapeutic Agents

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.132

I, David Munn do hereby declare the following:

1. I am an inventor of the claimed inventions disclosed in the above-referenced U.S. Patent Application Serial No. 10/660,131.

2. I am employed as a Professor of Medicine at the Medical College of Georgia. In conjunction with my ongoing research responsibilities, I have been actively engaged in research relating to elucidating the biochemical basis for the regulation of tolerance-inducing dendritic cells for over 10 years.

3. I have reviewed the Office Action mailed August 31, 2006, in the above-referenced patent application and, in particular, the Examiner's rejection of the pending claims as not being enabled under 35 U.S.C. § 112, first paragraph. In particular, I have reviewed the Examiner's assertions on pages 4-9 of the Office Action that the *in vitro* data provided by the specification does not enable use of CCR6 antagonists to reduce recruitment of IDO+ APCs to a particular site in an individual.

4. The *in vitro* assay used to measure mip-3α induced chemotaxis of CCR6+ APCs towards a gradient of mip-3α is an assay that is well-accepted by those in the field of chemokine research as a method to measure the specificity and efficacy of chemokine-induced migration,

and/or the inhibition of such chemokine-induced migration. Thus, it is accepted practice in the field of chemokine research to use this type of chemotaxis assay to predict chemokine-induced migration of dendritic cells that can occur *in vivo*. Examples of the use of this type of assay are provided by the following references: (1) Dieu et al., 1998, J. Exp. Med., 188:373-386; (2) Yang et al., 1999, Science 286: 525-528; and (3) Zou et al., 2001, Nature Medicine 7:1339-1346.

5. Further, the data in the patent specification confirms that the *in vitro* model used to measure chemotaxis of IDO+ APCs towards a mip-3α gradient accurately predicts the biologically relevant properties of the IDO+ cells found *in vivo*. Thus, the specification shows that at least some tumors and tumor-draining lymph nodes express mip-3α, and that IDO+ APCs are found in such mip-3α expressing tumors and/or tumor-draining lymph nodes.

6. Also, our subsequent work has shown that similar to what is shown in the specification for humans, immunosuppressive, tolerance-inducing DCs isolated from the tumor-draining lymph nodes of mice preferentially express CCR6 and CD123. In contrast, non-suppressive IDO-negative DCs from the same nodes express much lower levels of CCR6 and CD123 (see e.g., page 287 and Figure 7D of Munn et al., 2004, J. Clin. Invest., 114: 280-290). Also, it was found that murine IDO+ DCs isolated from tumor-draining lymph nodes suppress T cell responses *in vitro* in a manner similar to the inhibition shown for human CCR6+ DCs in the specification (see e.g., Munn et al., 2004 at page 281 and Figure 2). Thus, the studies in humans as described in the patent specification (i.e., the *in vitro* assays showing mip-3α induced chemotaxis of CCR6+ APCs; the ability of CCR6+ IDO+ APCs to reduce T cell proliferation; and the detection of IDO+ APCs and mip-3α expression in tumor samples and tumor-draining lymph nodes isolated from patients) predicted the *in vivo* expression of CCR6 and CD123 by murine IDO+ DCs in tumor-draining lymph nodes.

7. Also, when the murine IDO+CCR6+ DCs were injected into new, tumor-free mice, it was found that these cells were able to create an antigen-specific anergy in the host T cells (see e.g., Munn et al., 2004 at pages 282-283; Munn et al., 2005, Immunity 22:633-642 at page 638). Development of such antigen-specific anergy was prevented by the administration of the IDO inhibitor, 1-MT. Thus, the human *in vitro* system described in the patent application

correctly predicted the *in vivo* immunosuppressive and tolerogenic attributes of the murine counterpart of these cells.

8. It is known that mip-3α (i.e., CCR20) is the sole ligand of CCR6 in humans and mice. Thus, tumors that make mip-3α will preferentially recruit IDO+ DCs into their microenvironment.

9. All of these findings support our method of reducing recruitment of IDO+ APCs to tumors and tumor draining lymph nodes that express mip-3α. Thus, our claimed method recognizes that at least some tumors recruit CCR6-expressing IDO+ cells to the tumor and/or the tumor-draining lymph node to create a immunosuppresive milieu that favors tumor development due to IDO-mediated suppression of anti-tumor immunity.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

12.21.06
Date

Dr. David H. Munn, M.D.